5 Modifiers genes' influence in pulmonary disease in a group of Mexican patients with cystic fibrosis

M.D. Chavez[1,2], E. Yokoyama[1], V. Camilo[1], F. Cuevas[3], A. Carnevale[4], J. Lezana[5], M. Macias[6], L. Orozco[7]. [1]*Genetica Humana, INP, DF, Mexico;* [2]*UAM, Xochimilco, Mexico;* [3]*Neumologia, INP, DF, Mexico;* [4]*CNMG, ISSSTE, DF, Mexico;* [5]*HIM, DF, Mexico;* [6]*INP, DF, Mexico;* [7]*INMEGEN, DF, Mexico*

There are reports about the strong correlation between pancreatic function and the CFTR genotype, whereas others clinical signs could be different in patients with the same genotype. Because of this, it has been proposed the presence of modifiers genes that influence the severity of CF. The aim of this study is to determine the frequency of allelic variants of the genes TNF-α, MBL, α1AT, α1ACT, β-2AD, IL-10, NOS3 and their association with pulmonary disease. 60 patients with CF were included, 15 SNPs were analyzed by allelic discrimination with Taq-Man probes. Pulmonary phenotype was determined by positive Pseudomona cultures, health condition, age at diagnostic and death, beginning of symptoms, first positive Pae culture, Brasfield score and the best FEV1 in three years. The association of SNPs with the pulmonary disease was analyzed with the statistic program SPSS, an a value of $p < 0.05$. The distribution of genotypes was in equilibrium with Hardy-Weinberg. The frequency of allelic variants does not show differences with the literature reports. On the other hand significant differences were found in the variables MBL-550 with health condition, and α1ACT-15Thr>Ala with age at death and Brasfield score, and α1AT-Z with best FEV1 in three years. This is the first report about the association of some SNPs of specific response with variables of pulmonary phenotype among Mexican patients with CF. Our results suggest that genomic analysis of patients with CF could be necessary for predict the clinical evolution of the disease and to establish an individualized treatment of patients.

Supported by: INP:13/2004; CONACYT-SALUD 2003-C01–066.

6 The CFTR M470V gene variant as a potential modifier of COPD severity

M. Stankovic[1], A. Nikolic[1], A. Divac[1], A. Tomovic[2], N. Petrovic-Stanojevic[3], M. Andjelic[3], V. Dopudja-Pantic[3], M. Mitic-Milikic[4], D. Radojkovic[1]. [1]*Institute of Molecular Genetics and Genetic Engineering, Belgrade, Serbia;* [2]*Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland;* [3]*Zvezdara University Medical Center, Belgrade, Serbia;* [4]*Institute for Tuberculosis and Lung Disease, University Clinical Center of Serbia, Belgrade, Serbia*

Chronic Obstructive Pulmonary Disease (COPD) is a complex disease influenced by genetic and environmental factors. Different genetic variants may alter or modulate processes that could lead to initiation and progression of COPD pathogenesis.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein is an important component of the lung tissue homeostasis, involved in the regulation of the rate of mucociliary clearance. This study was undertaken to assess the role of F508del mutation and three common CFTR variants, M470V, IVS8–5T and R75Q, in COPD development and modulation. The presence of these variants was analyzed in 86 patients diagnosed with COPD and 102 control subjects and obtained results were subjected to statistical analysis.

No associations were detected between COPD development, onset of the disease and tested CFTR alleles and genotypes. However, VV470 genotype was associated with mild/moderate COPD stages in comparison to severe/very severe ones (OR = 0.29, 95% CI = 0.11–0.80, $p = 0.016$). Our study showed that patients with VV470 genotype had a 3.4-fold decreased risk for the appearance of severe/very severe COPD symptoms and the obtained results indicate that this genotype may have a protective role. Bearing in mind that advanced COPD is linked with clinical complications and diminished quality of life, this observation could be of special importance for prevention in mild/moderate COPD patients.

Supported by: EUROGENTEST, grant 143051 Ministry for Science, Republic of Serbia.

7 Analysis of eNOS, TNFA, LTA, GSTM1, MBL2, HFE genes as modifier genes in Russian cystic fibrosis patients

E.E. Timkovskaya[1], N.V. Petrova[1], N.J. Kashirskaya[1], R.A. Zinchenko[1]. [1]*Research Center for Medical Genetics, Moscow, Russian Federation*

Recent investigations have been established that polymorphic variants in genes besides CFTR play an important role in determining severity of CF disease. We analyzed the association of CF clinical features and polymorphisms/mutations in 6 genes: VNTR polymorphism in intron 4 of eNOS gene; −308 G–A of TNFA gene; +252 A–G of LTA gene; 10 kbp deletion polymorphism of GSTM1 gene; promoter polymorphism −221G–C and 3 mutations in exon 1, G54D, G57E, R52C, of MBL2 gene; C242Y and H63D of HFE gene in 148 CF patients homozygous for F508del mutation. Patients were categorized into groups according to their genotypes of analyzing genes. The age of lung and intestinal disease manifestation, the age of diagnosis, severity of disease progression, FVC and FEV1 indexes, height-weight indexes, *S. aureus* and *P. aeruginosa* colonization, liver disease and meconium ileus (MI) were evaluated. We revealed the association of eNOS, MBL2 and HFE genes and disease severity. Patients carrying A allele of the eNOS gene (genotypes A/A and A/B) had significantly lower pulmonary function ($p < 0.05$); airways colonization by *P. aeruginosa* were diagnosed significantly earlier in patients with MBL-insufficient alleles ($p < 0.02$); liver cirrhosis was more frequent among patients with B/B genotype of the eNOS gene ($p < 0.05$); and meconium ileus was more frequent in patients carrying D63 allele of HFE gene ($p < 0.05$). Associations between phenotypic characteristic of CF and analyzed polymorphisms of TNFA, LTA and GSTM1 genes were not found.

Supported by: Russian Found of Fundamental Researches (Grants 07-04-00090, 07-0410021, 05-04-48135).

8 The role of TGFbeta1 as modifier gene in Italian cystic fibrosis patients

M.D. Bettin[1], C. Bombieri[1], G. Malerba[1], L. Xumerle[1], F. Belpinati[1], C. Castellani[2], B.M. Assael[2], P.F. Pignatti[1]. [1]*DMIBG, University of Verona, Verona, Italy;* [2]*Cystic Fibrosis Veneto Regional Centre, Hospital of Verona, Verona, Italy*

Cystic fibrosis (CF) is a lethal, multi-system autosomal recessive genetic disorder primarily affecting Caucasian populations, caused by mutations in the CFTR gene. Severity of clinical presentation in CF, particularly the pulmonary manifestation, are highly variable. This variability is only partially explained by allelic heterogeneity at the CFTR gene. Literature data suggest that the severity in CF may be correlated with other genetic factors. Two polymorphisms (−509C/T and Leu10Pro) of the TGFB1 gene, which encodes for a cytokine involved in inflammation and tissue repair and expressed by several cells, have been associated to a more severe CF pulmonary manifestation in the American population (Drumm et al, NEJM 353:1443; 2005). We here report the results of association analyses of three TGFb1 polymorphisms (−509C/T, Leu10Pro, Arg25Pro) in Italian patients. Eighty family trios with a CF child and 52 unrelated CF patients were collected through the Veneto Regional CF Centre of Verona. All the patients were clinically evaluated for respiratory parameters, gastrointestinal and nutritional status parameters, and other clinical variables related to the common CF complications (diabetes, DIOS, etc). TDT test result showed evidence of association between Pro25 and FEV1 ($p = 0.018$). No association was found among other polymorphisms and studied clinical parameters. Single locus and haplotype analyses performed in all the unrelated CF patients confirm the association of TGFB1 gene polymorphisms with FEV1%.

These results compared to literature data indicate that further studies are necessary to characterized the involvement of TGFB1 gene as modifier of disease severity in CF.